## IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of

MacLEAN et al

Serial No. 08/776,350

Filed: April 18, 1997

Title: TREATMENT OF CANCER USING HSV MUTAN

Assistant Commissioner for Patents

Washington, DC 20231

Sir:

Atty Dkt. 620-73

C#/M#

Group Art Unit: 1642

Examiner: Unger

Date: February 10, 2000

SUPPLEMENTAL SUBMISSION

This is a response/amendment/letter in the above-identified application and includes an attachment which is hereby incorporated by reference and the signature below serves as the signature to the attachment in the absence of any other signature thereon.

### Fees are attached as calculated below:

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The Commissioner is hereby authorized to charge any <u>deficiency</u> in the fee(s) filed, or asserted to be filed, or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our **Account No. 14-1140.** A <u>duplicate</u> copy of this sheet is attached.

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Signature:

FEB 1 4 2000

## IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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For: TREATMENT OF CANCER USING HSV

**MUTANT** 

\* \* \* \* \* \* \* \* \*

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Assistant Commissioner of Patents Washington, DC 20231

Sir:

## SUPPLEMENTAL SUBMISSION

Supplemental to the Amendment of December 30, 1999, the applicants note, for completeness, that gliomas were incorrectly identified as being benign on page 6, penultimate line, of the Amendment. While it is true that gliomas are not "metastatic", such that they would not be included as a tumor to be treated by the presently claimed method, gliomas are not "benign". More specifically, gliomas are malignant while not being metastatic. See, the attached pages 162 and 771 of Dorland's Illustrated Medical Dictionary (26th Edition) 1981 W.B. Saunders Company, Philadelphia, PA.

One of-ordinary skill in the art would appreciate that gliomas are tumors that are produced in the brain from glial cells which are the normal supporting cells in the brain and that they are tumors which are restricted to the brain. Gliomas are not classified as metastatic tumors as they do not metastasize to other sites of the body. Upon removal by surgery, gliomas regrow

# 20 16) again in the brain and do not spread beyond the brain. Gliomas are characterized by over expression of glial fibrillary acidic protein (GFAP), which is a normal marker of glial cells. The over expression of GFAP is known as a characteristic of gliomas and changes which take place to transform normal glial cells into tumor cells are known to be contained entirely within the central nervous system and not elsewhere in the body.

Metastatic tumors, on the other hand, can arise from virtually all other types of malignant tumors in organs other than the brain. That is, metastatic tumors from the breast, lung, bowl, etc., can metastasize to other vital organs, including the brain. For instance, it is common for breast tumors and melanomas to metastasize to the brain. Metastasis is, therefor, a generalized process, usually with multiple foci of metastases, arising from a single primary tumor at an unrelated site. Sometimes, cancer is only diagnosed when a metastasized tumor produces problems. Metastatic cancer cells have the capacity to spread throughout the body and this is quite different from glioma cells which are entirely restricted to the brain.

One of ordinary skill would also appreciate that the cell markers of tumors are different and depend from the origin of the tumor. Metastasized tumors will have different expression patterns and different pathology, depending on the pathology of the primary tumor. Gliomas will always have the same pathology and the same markers. In others words, when a brain tumor is diagnosed on a scan and a biopsy is taken for pathology, there is an unambiguous distinction between a glioma and metastatic brain tumor arising from, for example, a primary breast tumor.

Accordingly, gliomas are not within the scope of tumors treated by the presently claimed method and the inadvertent error in referring to gliomas as "benign" is regreted.

# U.S. Patent Application of *MacLEAN et al* Serial No. 08/776,350

An early and favorable Action on the merits is requested.

Respectfully submitted,

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By:

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gastric muscle, venter anterior musculi digastrici. delhi b., a dysenteric infection occurring in tropical countries, manifested as an acute diarrheal disease. drum b., tympanitic abdomen. frontal b. of occipitofrontal muscle, venter occipitalis musculi occipitofrontal b. of occipitofrontal muscle, venter occipitalis musculi occipitofrontalis. posterior b. of digastric muscle, venter posterior musculi digastrici. prune b., see under syndrome. swollen b., tympanites in animals. wooden b., abdominal rigidity.

belonoid bel'o-noid) [Gr. belone needle + eidos form] needle-shaped; styloid.

belonoskiascopy (bel"o-no-ski-as'ko-pe) [Gr. belone needle + skia shadow + skopein to examine] a method of retinoscopy.

beloxamide (bel-oks'ah-mīd) chemical name: N-(benzyloxy)-N(3-phenylpropyl)acetamide; an anticholesteremic agent, C<sub>18</sub>-H<sub>21</sub>NO<sub>2</sub>.

belt (belt) an encircling band worn about the waist or abdomen; called also balteum. Cf. girdle.

bemegride (bem'&grid) chemical name: 4-ethyl-4-methyl-2,6-piperidinedione. An analeptic drug, C<sub>0</sub>H<sub>13</sub>NO<sub>2</sub>, which has been used in the treatment of barbiturate poisoning.

bemidone (bem/l-don) chemical name: ethyl 4-(m-hydroxyphenyl)-1-methylisonipecotate. A crystal compound, C<sub>15</sub>H<sub>2</sub>NO<sub>3</sub>, soluble in water; formerly used as a narcotic and analgesic.

benactyzine hydrochloride (ben-ak/tĬ-zēn) chemical name: α-hydroxy-α-phenylbenzeneacetic acid 2-(diethylamino)ethyl ester hydrochloride. An anticholinergic, C<sub>20</sub>H<sub>20</sub>ClNO<sub>3</sub>, occurring as a white. crystalline powder, which has the ability to increase the emotional threshold of outside influences and to block the thought processes; used as a tranquilizer, administered orally.

Benadryl (ben'ah-dril) trademark for preparations of diphenhydramine hydrochloride.

benapryzine hydrochloride (ben-ah-pri/zēn) chemical name: 2(ethylpropylamino)ethyl benzilate hydrochloride; an anti-cholinergic, C<sub>21</sub>H<sub>27</sub>NO<sub>3</sub>·HCl.

Bence Jones protein, etc. [Henry Bence Jones. English physician, 1814-1873] see under cylinder, protein, proteinuria, and reaction

bend (bend) a flexure or curve; a flexed or curved part. first order b's, adjustments made in a labial arch wire, incorporating offsets in the horizontal plane, which are usually made in the areas of the cuspids and premolar and molar teeth, accommodating differences in thickness in the labiolingual or buccolingual diameters of the teeth. head b., cephalic flexure. neck b., cervical flexure. second order b's, bends in the vertical plane of an arch wire. third order b's, bends in an arch wire to maintain or produce torsion of a tooth. V b's, V-shaped bends incorporated in an arch wire, usually placed mesial or distal to the cuspids to improve the axial relationship of teeth. varolian b., the third cerebral flexure in the developing fetus.

bendazac (ben'dah-zak) chemical name: [(1-benzyl-1 H-indazol-3-yl)oxy]acetic acid; an anti-inflammatory agent, C<sub>16</sub>H<sub>14</sub>-N<sub>1</sub>O<sub>1</sub>

Bendectin (ben-dek'tin) trademark for tablets containing a combination of dicyclomine hydrochloride, doxylamine succinate, and pyridoxine hydrochloride; used in management of nausea and parties during programment.

vomiting during pregnancy.

bendrofluazide (ben"dro-floo'ah-zid) bendroflumethiazide.

bendroilumethiazide (ben"dro-floo"mĕ-thi'ah-zīd) [USP] chemical name: 3,-dihydro-3-(phenylmethyl)-6-(trifluoromethyl)-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide. A white to cream-colored crystalline powder, C<sub>15</sub>H<sub>14</sub>F<sub>2</sub>N<sub>3</sub>O<sub>4</sub>S<sub>2</sub>, used as an oral diuretic and antihypertensive.

**bends** (bendz) pain in the limbs and abdomen occurring as a result of rapid reduction of air pressure; see *decompression sickness*, under *sickness*.

Bendylate (ben'dĭ-lāt) trademark for preparations of diphenhydramine hydrochloride.

bene (be'ne) [L.] well.

beneceptor (ben'e-sep-tor) [L. bene well + ceptor] a rarely used term for a receptor that transmits stimuli of a beneficial character. Cf. nociceptor and ceptor, def. 2.

Beneckea (be-nek'e-ah) a genus of microorganisms of the family Achromobacteraceae, order Eubacteriales, made up of small to medium-sized rods, found in salt and fresh water and soil, which may or may not be chromogenic. It includes six species. B. chitino'vora, B. hyperop'tica, B. indolthe'tica, B. la'bra, B. lipo'-phaga, and B. ureaso'phora.

Benedict's test (ben'e-dikts) [Stanley Rossiter Benedict, American physiological chemist, 1884-1936] see under tests.

Benedict-Hopkins-Cole reagent (ben'ĕ-dikt-hop'kinz-kōl) [Stanley Rossiter Benedict: Sir Frederick Gowland Hopkins, English biologist, 1861–1947; Sidney William Cole, English physiologist, born 1877] see under reagent.

Benedikt's syndrome (ben'e-dikts) [Moritz Benedikt, Austrian physician, 1835-1920] see under syndrome.

benign 'be-nīn') [L. benignus] not malignant; not recurrent; [a. vorable for recovery.

benignant (be-nig'nant) benign.

Béniqué's sound (ba-ne-kāz') [Pierre Jules Béniqué, French phy. sician, 1806-1851] see under sound.

Benisone (ben/1-son) trademark for preparations of betamethasone benzoate.

benjamin (ben'jah-min) benzoin, def. 1.

Bennet's corpuscles (ben'ets) [James Henry Bennet, English obstetrician, 1816-1891] see Nunn's gorged corpuscles and Drysdale's corpuscles, under corpuscle.

Bennett's disease (ben'ets) [John Hughes Bennett, English physician, 1812-1875] leukemia.

Bennett's fracture, operation (ben'ets) [Edward Hallaran Bennett, Irish surgeon, 1837-1907] see under fracture and operation.

Benoquin (ben'o-kwin) trademark for preparations of monobenzone.

benorterone (bě-nor'ter-ōn) chemical name: 17β-17-hydroxy-17-methyl-B-norandrost-4-en-3-one; an antiandrogen, C<sub>10</sub>H<sub>20</sub>O<sub>1</sub>.

benoxaprofen (ben-oks"ah-profen) chemical name: 2-(4-chlo-rophenyl)-a-methyl-5-benzoxazoleacetic acid; an anti-inflammatory and analgesic, C<sub>10</sub>H<sub>12</sub>ClNO<sub>3</sub>.

benoxinate hydrochloride (ben-ok'sI-nāt) [USP] chemical name: 4-amino-3-butoxybenzoic acid 2-(diethylamino)ethyl ester monohydrochloride. A local anesthetic, C<sub>17</sub>H<sub>28</sub>N<sub>2</sub>O<sub>2</sub>-HCl, occurring as white crystals or as a white, crystalline powder; used in ophthalmology, applied topically to the conjunctiva.

Benoxyl (ben-ok'sil) trademark for preparations of benzoyl per-

benserazide (ben-ser'ah-zid) chemical name: 2-[(2,3,4-trihy-droxyphenyl)-methyl]hydrazide DL serine; a decarboxylase inhibitor,  $C_{10}H_{1s}N_3O_3$ .

Benson's disease (ben'sunz) [Alfred Hugh Benson, Irish ophthal mologist, 1852-1912] asteroid hyalosis.

bentazepam (ben-taz/ĕ-pam) chemical name: 1,3,6,7,8,9-hex-ahydro-5-phenyl-2H-[1]benzothieno[2,3-e]-1,4-diazepin-2-one: a tranquilizer,  $C_{17}H_{16}N_2OS$ .

benthos (ben'thos) [Gr. benthos bottom of the sea] the flora and fauna of the bottom of oceans.

bentonite (ben'ton-it) [NF] a native, colloidal, hydrated aluminum silicate, which on the addition of water swells to produce a slippery paste; its chief pharmaceutical use is as a suspending agent, and it has also been used as a bulk laxative.

Bentyl (ben'til) trademark for preparations of dicyclomine by drochloride.

benzaldehyde (ben-zal/dĕ-hīd) [NF] artificial essential oil almond; used as a flavoring agent in orally administered medicaments.

benzalin (ben'zah-lin) nigrosin.

benzalkonium chloride (ben"zal-ko'ne-um) [NF] a mixtum of alkylbenzyl dimethylammonium chlorides of the general for mula, [C<sub>4</sub>H<sub>2</sub>CH<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>R|Cl. A rapidly acting surface disinfectand and detergent, occurring as a white or yellowish white, thick sor gelatinous pieces, which is active against both gram-negative and gram-positive bacteria and certain viruses, fungi, yeasts, approtozoa; applied topically to the skin and mucous membranes is also used as an antimicrobial preservative in ophthalms solution.

benzamidase (ben-zam/i-dās) an enzyme that catalyzes the change of benzoic acid into benzamide.

benzamine (ben'zah-men) eucaine.

benzanthracene (ben-zan'thrah-sēn) one of a group of hydrocarbons some of which have carcinogenic properties.

benzazoline hydrochloride (benz-az/o-lēn) tolazoline by drochloride.

benzbromarone (benz-bro/mah-rŏn) chemical name: (3.5-0 bromo-4-hydroxyphenyl)-(2-ethyl-3-benzofuranyl)methanone: uricosuric drug, C<sub>17</sub>H<sub>12</sub>Br<sub>2</sub>O<sub>3</sub>.

benzeurine iodide (benz'ku-rēn) gallamine triethiodide.

Benzedrex (ben'zĕ-dreks) trademark for a propylhexedrine in haler.

Benzedrine (ben'zĕ-drēn) trademark for preparations of sphetamine sulfate.

benzene (ben'zēn) a colorless volatile liquid hydrocarbon, C. It obtained mainly as a by-product in the destructive distillation coal, along with coal tar, etc. It has an aromatic odor, and bur with a light-giving flame. It dissolves sulfur, phosphorus, iodinand organic compounds. The fumes may cause fatal poisoning was formerly used as a pulmonary antiseptic in influenza, etc., a teniacide, externally as a parasiticide, and has been suggested leukemias. Called also benzol. dimethyl b., xylene. hexachloride, chemical name: 1,2,3,4,5,6-hexachlorocyclohane. A compound, C. H. Cl., prepared by chlorination of benzene action light consisting of five isomers, the gamma isomer being

cic (mah-la'sik) marked by malacia or morbid softness. co-\*[Gr. malakos soft] a combining form meaning a condiof abnormal softness.

coma (mal"ah-ko'mah) [malaco- + oma] a morbidly soft t or spot.

coplakia (mal"ah-ko-pla'ke-ah)[malaco- + Gr. plax plaque] formation of soft patches on the mucous membrane of a hollow m. vesi'cae, a soft, yellowish, fungus-like growth on mucous membrane of the bladder and ureters.

cosarcosis (mal"ah-ko-sar-ko'sis) [malaco- + Gr. sarx flesh] ess of muscular tissue.

cosis (mal"ah-ko'sis) malacia.

costeon (mal"ah-kos'te-on) [malaco + Gr. osteon bone]

otic (mal"ah-kot'ik) inclined to malacia; soft; said of

tic (mah-lak'tik) 1. softening; emollient. 2. an emollient

ie (mal"ah-de") [Fr.] a disease. m. bleue, morbus caerie man ander (Fr.) a disease. m. bieue, morous caer-m. de Capdepont, dentinogenesis imperfecta. m. jambes (da-zhamb'), a disease of rice growers in Louisiana, ibly beriberi. m. de Nicolas et Favre, lymphogranuvenereum. m. de plongeurs (duh-plon-zher'), inflamn and ulceration in divers in the Mediterranean caused by ings of sea anemones. m. de Roger, Roger's disease. u sommeil (du-so-ma'e), African trypanosomiasis. m. tics, Gilles de la Tourette syndrome.

justment (mal"ad-just'ment) ation to environment, marked by anxiety, depression, and in psychiatry, defective hility.

y (mal'ah-de) [Fr. maladie] any disease or illness.

ma (mah-lag'mah) [Gr.] an emollient or cataplasm. ⇒ (mal-āz') [Fr.] a vague feeling of bodily discomfort.

oplakia (mal"ah-ko-pla'ke-ah) malacoplakia.

gnment (mal"ah-lin'ment) displacement out of line, esly displacement of the teeth from their normal relation to e of the dental arch.

gement (mal"ah-lin'ment) malalignment.

(ma'lar) [L. mala cheek] pertaining to the cheek or cheek

3 (mah-la're-ah) [It. "bad air"] an infectious febrile disaused by protozoa of the genus Plasmodium, which are tic in the red blood cells, and are transmitted by the bites the in the state of the genus Anopheles. The disease is terized by attacks of chills, fever, and sweating, occurring rvals which depend on the time required for development w generation of parasites in the body. After recovery from ute attack, the disease has a tendency to become chronic, casional relapses. algid m., falciparum malaria chared by peripheral vascular failure, with coldness of the skin, tion, and extensive involvement of the vessels of the ntestinal tract and other abdominal viscera. benign n m., vivax m. bilious remittent m., a pernicious falciparum malaria characterized by severe nausea, al vomiting, high remittent fever, and jaundice appearing he second day after onset. bovine m., Texas fever. al m., falciparum malaria with delirium or coma, as a localization of parasites (parasitic thrombus) in the brain. ., algid m. m. comato'sa, cerebral malaria charac-by coma. dysenteric m., falciparum malaria characby bloody diarrhea. estivoautumnal m., former r falciparum malaria when it was endemic in the United falciparum m., the most serious form of malaria. y Plasmodium falciparum, characterized by severe constisymptoms and sometimes causing death. gastric m., um malaria in which there is continual vomiting. he-m., blackwater fever. hemorrhagic m., falcipalaria in which hemorrhage is a prominent symptom. 1 m., malaria that is purposely produced by introduction usative parasites, as sometimes used in treating neuromalignant tertian m., falciparum m. ovale m., sease caused by infection with Plasmodium ovale, usually rized by a few regularly recurring tertian febrile parox-sinning with a feeling of chilliness or cold shivers rather rigors typical of vivax malaria, and tending to end aneous recovery. pernicious m., falciparum m. m., that in which the febrile paroxysms occur every 72 every fourth day counting the day of occurrence as the of each cycle; it is caused by Plasmodium malariae, which 72 hours for completion of each asexual cycle in the te. quotidian m., that in which the febrile paroxir daily, due to simultaneous infection with two broods of am vivax, which complete their 42- to 47-hour cycle on days. See vivax m. subtertian m., falciparum m. m., that in which the febrile paroxysms occur every 42 rs, or every third day counting the day of occurrence as lay of the cycle. See vivax m. therapeutic m., invivax m., malaria caused by Plasmodium vivax. most common and most likely to recur; the febrile

paroxysms commonly occur every other day (tertian m.), but may occur daily (quotidian m.), if there are two broods of parasites segmenting on alternate days.

malariacidal (mah-la"re-ah-si'dal) destructive to malarial plasmodia; plasmodicidal.

malarial (mah-la/re-al) pertaining or due to malaria.

malariatherapy (mah-la"re-ah-ther'ah-pe) malariotherapy. malariologist (mah-la"re-ol'o-jist) a person versed in or engaged in the study of malaria.

malariology (mah-la"re-ol'o-je) [malaria + -logy] the study of

malariometry (mah-la"re-om'e-tre) the employment of quantitative methods in the study of malaria.

malariotherapy (mah-la"re-o-ther'ah-pe) mentia paralytica by infecting the patient with malarial parasites. usually the parasite of tertian malaria (Plasmodium vivax) or of quartan malaria (P. malariae).

malarious (mah-la're-us) pertaining to or marked by the pres-

malaris (mah-la'ris) [L.] malar.

Malassez's disease, rests (mal"ah-saz') [Louis Charles Malassez, physiologist in Paris, 1842-1909] see under disease and

Malassezia (mal"ah-se'ze-ah) [Louis Charles Malassez] Pityrosporon. M. furfur, M. macfadyani, M. tropica, Pityrospo-

malassimilation (mal"ah-sim"ī-la'shun) [L. malus ill + similatio a rendering like] 1. imperfect, faulty, or disordered assimiliation. 2. the inability of the gastrointestinal tract to transport to the body fluids one or more ingested nutrients, whether due to faulty digestion (maldigestion) or to impaired intestinal mucosal transport (malabsorption).

malate (ma'lat) any salt of malic acid; in biochemistry, the term is often used interchangeably with malic acid (see under

malathion (mal"ah-thi'on) chemical name: O.O-dimethyl-S-(1,2-dicarboxyethyl)dithiophosphate. An organophosphorus compound used as an insecticide.

malaxate (mal'ak-sât) to knead, as in making pills.

malaxation (mal"ak-sa'shun) [Gr. malaxis a softening] an act

Malcotran (mal/ko-tran) trademark for a preparation of hom-

maldevelopment (mal"de-vel'op-ment) abnormal growth or

maldigestion (mal"di-jes'chun) impaired digestion.

male (mal) 1. an organism of the sex that begets young or that produces spermatozoa. 2. masculine.

maleate (mal'e-āt) any salt or ester of maleic acid.

malemission (mal"e-mish'un) failure of the semen to be discharged from the urinary meatus in coitus.

Malerba's test (mah-ler'bahz) [Pasquale Malerba, Italian physician, 1849-1917] see under tests.

maleruption (mal"e-rup'shun) faulty eruption of a tooth, so that it is out of its normal position.

malethamer (mal-eth'ah-mer) a high weight copolymer of ethylene with maleic anhydride, cross-linked with  $1\ {
m to}\ 2$  per cent, by weight, of vinyl crotonate; an antiperistalic agent.

malformation (mal"for-ma'shun) [L. malus evil + formatio a forming] defective or abnormal formation; deformity; an anatomical aberration, especially one acquired during development. Arnold-Chiari m., see under deformity.

malfunction (mal-funk'shun) dysfunction.

Malgaigne's amputation, etc. (mal-ganz') [Joseph François Malgaigne, French surgeon, 1806-1865] see under amputation. hook, luxation, pad, and triangle.

maliasmus (mal"e-as'mus) glanders, or farcy.

malignancy (mah-lig'nan-se) [L. malignare to act maliciously] a tendency to progress in virulence; the quality of being malig-

malignant (mah-lig'nant) [L. malignans acting maliciously] tending to become progressively worse and to result in death Having the properties of anaplasia, invasion, and metastasis; said of tumors.

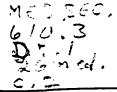
malignin (mah-lig'nin) a protein fragment present in the serum of patients with malignant glial tumors.

malignogram (mah-lig'no-gram) a systematic arrangement of numerical values assigned to the various factors in cases of

mali-mali (mah"le-mah'le) a form of saltatory spasm endemic in the Philippines.

malingerer (mah-ling/ger-er) [Fr. malingre sickly] an individual who is guilty of malingering.

malingering (mah-ling'ger-ing) the willful, deliberate, and



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